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CERTIFICATE EXPRESS MAILING

NUMBER: EV 918 016 487 US

DATE: August 7, 2006

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MAIL STOP APPEAL BRIEF-PATENTS

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Re: U. S. Patent Application Serial No. 10/790,658 entitled "R(-)-Desmethylselegiline and Its Use to Treat Immune System Dysfunction" by Cheryl D. Blume, *et al.*
(Our Ref: SOM700/4-4CIP2CON2DIVUS/13004)

Dear Sir:

Enclosed for filing in the above-referenced patent application are the following:

1. Reply Brief in triplicate (25 pages each); and
2. Postcard.

If additional fees are due related to this filing, the Commissioner is authorized to appropriately deduct the requisite amount from Vinson & Elkins L.L.P. Deposit Account No. 22-0365/SOM700/4-4CIP2CON2DIVUS/13004.

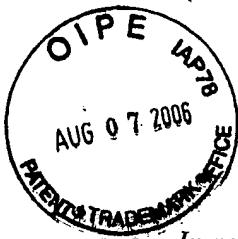
Very truly yours,

Margaret J. Sampson

MJS/cp
Enclosures

08-09-06

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ZMW



PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Cheryl D. Blume *et al.*

Serial No.: 10/790,658

Filed: March 1, 2004

For: R(-)-DESMETHYLSELEGILINE AND
ITS USE TO TREAT IMMUNE SYSTEM
DYSFUNCTION

Group Art Unit: 1615

Examiner: L.S. Channavajjala

Atty. Dkt. No.: SOM700/4-
4CIP2CON2DIVUS/13004

Confirmation No.: 9575

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REPLY BRIEF

MAIL STOP APPEAL BRIEF-PATENTS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Examiner's Answer mailed June 5, 2006, Appellant now submits this Reply Brief.

I. REAL PARTY IN INTEREST

The real party in interest of the patent application that is the subject of this appeal is the assignee, Somerset Pharmaceuticals, Inc.

II. RELATED APPEALS AND INTERFERENCES

At the time the present Appeal was filed, appeals were pending in the following two applications, which are also assigned to Somerset Pharmaceuticals, Inc. Recently, however, the Examiner issued a Notice of Allowance for each application. Therefore, appeals are no longer pending for the following two applications.

1. Serial No. 10/885,221, Anthony R. DiSanto, filed July 6, 2004.
2. Serial No. 10/806,494, Mark G. Resnick, filed March 3, 2004.

III. STATUS OF CLAIMS

Claims 26 and 34-62 are pending in the instant application and are the subject of this Appeal. Claims 26 and 34-62 stand rejected by the Examiner.

IV. STATUS OF AMENDMENTS

None

V. SUMMARY OF CLAIMED SUBJECT MATTER

Appellant's application contains independent claims 26, 43 and 46. Claim 26 recites a method of treating a condition in a mammal produced by immune system dysfunction that is associated with reduced levels of gamma-interferon (" γ -interferon") production by administering to the mammal the R(-)-enantiomer of desmethylselegiline, or a pharmaceutically acceptable salt thereof (Specification, p.8, ll.21-22), at a daily dose of at least 0.015 mg/kg of the mammal's body weight, calculated on the basis of the free secondary amine (*Id.* at p.9, ll.12-16), wherein such administration leads to an increase in γ -interferon production in the mammal. *See, e.g., id.* at p.39, ll. 12-14. The daily dose may be administered in either a single or multiple dosage regimen. *Id.* at p.9, 1.22.

Claim 43 recites a method of treating a condition in a mammal produced by immune system dysfunction caused by cancer chemotherapy which is associated with reduced levels of γ -interferon production by administering to the mammal the R(-) enantiomer of desmethylselegiline, or pharmaceutically acceptable salts thereof (*Id.*, p.8, ll.21-22), at a daily dose of at least 0.015 mg/kg of the mammal's body weight, calculated on the basis of the free secondary amine (*Id.* at p.9, ll.12-16), wherein such administration leads to an increase in γ -interferon production in the mammal. *See, e.g., id.* at p.39, ll. 12-14. The daily dose may be administered in either a single or multiple dosage regimen. *Id.* at p.9, 1.22.

Claim 46 recites a method of treating a condition in a mammal produced by immune system dysfunction that is associated with reduced levels of γ -interferon production by administering to the mammal the R(-) enantiomer of desmethylselegiline, or a pharmaceutically acceptable salt thereof (*Id.*, p.8, ll.21-22), wherein such

administration leads to an increase in γ -interferon production in the mammal. *See, e.g.*,
id. at p.39, ll. 12-14.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Whether claims 26 and 34-62 are unpatentable under 35 U.S.C. § 112 for lack of enablement.
2. Whether claims 26 and 34-62 are unpatentable under 35 U.S.C. § 103(a) as obvious over Borbe (J. Neural. Transm. Suppl. 1990) in view of Barton et al (J. Neurooncol.) and Balsa et al (Biochem. Pharmacol. 1987).

VII. ARGUMENT

A. The Rejection Based on 35 U.S.C. § 112, First Paragraph, for Lack of Enablement Should Be Overturned.

Appellant hereby incorporates by reference and relies upon all of the arguments presented in its Appeal Brief filed March 16, 2006. In order to facilitate review by the Board, Appellant also presents the following arguments which outline the central deficiencies in the enablement rejection maintained by the Examiner's Answer.

Claims 26 and 34-62 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. In the Examiner's Answer (the "Answer"), the Examiner continues to inappropriately focus on the underlying complexity of the immune system and the conditions treated to argue that the claimed methods are not enabled. Under the proper standard for enablement, the present claims are in compliance with 35 U.S.C. § 112, ¶1, because the claimed methods can be performed without undue experimentation. This is because it is well within the skill of one in the art to determine whether a condition produced by immune system dysfunction is associated with reduced levels of γ -interferon production, and whether administering R(-)-desmethylselegiline, or a pharmaceutically acceptable acid addition salt thereof, leads to an increase in γ -interferon production.

In the Answer, the Examiner ignores the legal standard for evaluating enablement and instead invents a series of "requirements" that are not supported by the text of 35 U.S.C. § 112 or case law. The Federal Circuit has stated that the proper test for evaluating enablement under 35 U.S.C. § 112, ¶1, is whether or not a patent application "teach[es] those in the art to make and use the invention without undue experimentation." *E.g. In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Although the Examiner obliquely

references several *Wands* factors in her rejection, she ignores the undue experimentation standard described in *Wands* to maintain the rejection. Rather than focusing on the language of the claims and the specification to determine if the claimed methods can be practiced by one of skill in the art without undue experimentation, the Examiner maintains that Appellant's claims are not enabled by setting forth a series of "requirements" that go beyond the information necessary to meet the enablement requirement for patentability.

When evaluating the enablement requirement, the fact that the claims are directed to methods of treating certain conditions with a therapeutic agent, R(-)-desmethylselegiline, must be kept in mind. As set forth in more detail in Part A.1 below, special considerations apply to the application of the utility requirement to pharmaceutical and therapeutic inventions. The utility requirement for this class of inventions only requires a reasonable correlation between the activity of the compound and the claimed use. This is based on the rationale that the development of pharmaceutical drugs is very beneficial to the public, and the understanding that such development takes considerable time and resources. Considering the time and resources necessary to commercialize a therapeutic agent, the patent law has recognized the patentability of these inventions in their early stages. The same policy and rationale should guide the application of the enablement requirement to such inventions. Significantly, the issue of "correlation" is also a factor under the enablement requirement.

See MPEP § 2164.02.

The following "requirements" set forth by the Examiner to prove enablement are simply unreasonable for a pharmaceutical and therapeutic invention:

- Appellant has not shown that “one of an ordinary skill in the art would readily recognize that a particular condition... is *always* associated with reduced levels of gamma-interferon.” Examiner’s Answer, p. 10 (emphasis added).
- Appellant has not shown that the conditions which may be treated using the presently claimed methods are caused by decreased “levels of gamma-interferon *alone*.” *Id.* at pp. 10-11 (emphasis added).
- Appellant has not provided “enough guidance to readily determine the effective amount of R(-) DMS to achieve the therapeutic effect... because the description only provides a *general statement* of optimizing the dosage depending on the severity of disease or condition.” *Id.* at p. 11 (emphasis added).
- Appellant has not shown how “to treat *all conditions* associated with the reduced levels of IFN-gamma and provide a therapy for the same.” Examiner’s Answer, p. 12 (emphasis added).
- Appellant has not shown that the exemplary conditions identified by Appellant “*per se can be treated* by improving or increasing the levels of gamma-IFN.” *Id.* at p. 12 (emphasis added).
- Appellant has not shown that “an increase [in γ -interferon levels] *definitely* treats the claimed conditions.” *Id.* at p. 13 (emphasis added).

Appellant has clearly established a reasonable correlation between the activity of the compound and the claimed methods, as well as enabled the claimed methods. The above “requirements” go beyond the information Appellant can and must supply at this early stage to establish the patentability of the claimed subject matter. In addition, the

Examiner has provided no evidence upon which to question the veracity of any statement in Appellant's Specification, nor provided any evidence which refutes or contradicts Appellant's stated correlation. *See MPEP § 2164.04; Application of Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971).

1. *The Examiner's requirements are inconsistent with highly relevant case law related to the utility requirement for pharmaceutical inventions*

The Examiner has failed to identify any case law which suggests or explains the applicability of her "requirements" to the enablement of the claimed methods. Furthermore, the Examiner's "requirements" are, in fact, inconsistent with the MPEP and case law dealing with the utility requirement for pharmaceutical inventions.¹

MPEP §§ 2107.01 and 2107.03 discuss special considerations that apply to the application of the utility requirement to pharmaceutical and therapeutic inventions. MPEP § 2107.03 states that a patent applicant "does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans." MPEP § 2107.03(I) (citing *Nelson v. Bowler*, 626 F.2d 853, 857 (C.C.P.A. 1980)). Instead a reasonable correlation between the activity of a compound and a claimed use will establish utility. *Id.* The rationale underlying this policy is that knowledge of pharmacological activity of compounds is immediately beneficial to the public and therefore a strong incentive should exist to encourage research aimed at identifying and developing such products. *See, e.g.*, MPEP

¹ The relevance of the case law and MPEP provisions dealing with the utility requirement, as applied to pharmaceutical inventions, to the enablement requirement for pharmaceutical inventions is supported by the MPEP which, under the heading "III. Drug Cases", refers to sections 2107–2107.03, which are related to the utility requirement under 35 U.S.C. § 112.

§ 2107.01(III). Importantly, this policy recognizes that further research and development will be necessary for pharmaceutical products after the point at which they become patentable as compositions or methods of treatment. *See, e.g. In re Brana*, 51 F.3d 1560, 1565-68 (Fed. Cir. 1995).

The Federal Circuit has clearly instructed that the stage at which pharmaceutical products become useful in the patent law context is typically well before the time those products are ready to be administered to humans. *See In re Brana*, 51 F.3d 1560, 1568 (Fed. Cir. 1995). Appropriately, any concerns related to the efficacy of a claimed method or composition should be left to the Food and Drug Administration (“FDA”). *See, e.g., Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994). If proof of efficacy were required as a prerequisite for patentability, the costs and risks associated with developing such proof would prevent many companies from pursuing patent protection for pharmaceutical products, thereby defeating the incentive to encourage research and development of beneficial pharmaceutical products. *See, e.g., Brana*, 51 F.3d at 1568.

The policy and rationale that guides the application of the utility requirement to pharmaceutical inventions is a useful and appropriate guide for analyzing enablement of the claimed methods. The proper enablement requirement does not require Appellant to show: (1) “that a particular condition... is *always* associated with reduced levels of gamma-interferon”; (2) conditions are caused by decreased “levels of gamma-interferon *alone*”; (3) how “to treat *all conditions* associated with reduced levels of IFN-gamma”; (4) conditions “*per se can be treated* by improving or increasing the levels of gamma-IFN”; and (5) “an increase [in γ -interferon levels] *definitely* treats the claimed conditions.” Examiner’s Answer, pp. 10-13 (emphasis added). The Examiner should not

be permitted to contravene the purpose of permitting patents to issue on early-stage pharmaceutical inventions by inventing enablement “requirements” which require an exhaustive understanding of the biological mechanism(s) by which the therapeutic agent functions, as well as the efficacy of the agent in humans.

2. *Appellant has presented a reasonable correlation between the activity of R(-)-desmethylselegiline and the claimed methods, and the Examiner has failed to provide any evidence which contradicts this correlation*

The issue of “correlation” is also a factor under the enablement requirement. See MPEP § 2164.02. Appellant has presented a working example in the Specification that correlates the activity of R(-)-desmethylselegiline to the claimed methods. The experimental data shows that R(-)-desmethylselegiline can be used to increase γ -interferon production levels in old rats with an age-related decline in immune system and γ -interferon production. Specification, Example 11, pp. 38-41. The Specification further states that in light of this finding, R(-)-desmethylselegiline will be useful for the treatment of conditions associated with weakened immunity. *Id.* at p. 41. As already set forth, γ -interferon plays a central role in the immune system, and immune system dysfunction related to γ -interferon has been recognized in both immune deficiency and autoimmune diseases. Billiau, A., *Interferon- γ : Biology and Role in Pathogenesis*, ADV. IMMUNOL. 62:61-130 (1996). Based on the ability of R(-)-desmethylselegiline or a salt thereof to increase γ -interferon production, one of skill in the art would correlate using R(-)-desmethylselegiline to treat certain conditions produced by immune system dysfunction, *i.e.* those associated with reduced levels of γ -interferon production. The Examiner has failed to offer any evidence to rebut this correlation.

3. *Appellant has presented sufficient guidance to one of skill in the art to determine the effective amount of R(-)-desmethylselegiline to achieve the therapeutic effect, and the Examiner has failed to rebut this conclusion*

The Examiner argues that the Appellant has not provided “enough guidance to readily determine the effective amount of R(-) DMS to achieve the therapeutic effect... because the description only provides a general statement of optimizing the dosage depending on the severity of disease or condition.” *Id.* at p. 11. But the teachings of the specification on the proper dosage and administration of R(-)-desmethylselegiline (*See* Specification, p.9, 1.8 to p.10, 1.20) are sufficient for one of skill in the art to readily determine the required amount of R(-)-desmethylselegiline necessary to achieve a therapeutic response based on animal studies and early stage clinical trials, both of which are standard in the field and permissible under MPEP § 2164.01(c). In response, the Examiner offers only conclusory assertions to support her argument, which are insufficient to meet her burden: “In order to make a rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention.” MPEP § 2164.04 (citing *In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993)). The Examiner has not established any such reasonable basis.

4. *The experimentation necessary to perform the claimed methods is not undue in light of the Specification and claim language*

The enablement standard requires a patent applicant to explain how to make and use an invention in such a way that a person of ordinary skill in the art can practice the invention without undue experimentation. *See Wands*, 858 F.2d at 737. Appellant asserts that the claimed methods are enabled because it is well within the skill of one in the art to determine whether a condition produced by immune system dysfunction is associated with reduced levels of γ -interferon production, and whether administering the

R(-)-desmethylselegiline or a salt thereof leads to an increase in γ -interferon production. The claimed methods of treatment require nothing more than the performance of routine tasks well within the knowledge and experience of a person of skill in the art. Importantly, a “patent need not teach, and preferably omits, what is well known in the art.” MPEP § 2164.01 (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991)).

In the Answer, the Examiner fails to provide a reasoned response to Appellant’s argument that the claims are enabled because no undue experimentation is required to practice the claimed methods. Instead, the Examiner focused on the underlying complexity of the immune system and the conditions treated according to the claimed methods to set forth the previously-identified series of unreasonable “requirements” to meet the enablement requirement, without any case law support. This style of response by the Examiner must be rejected.

In light of these arguments, and the arguments in Appellant’s original Appeal Brief, Appellant respectfully requests that the Board overturn the Examiner’s rejection and allow the pending claims.

B. The Obviousness Rejection Under 35 U.S.C. § 103 Should Be Overturned

Appellant hereby incorporates by reference and relies upon all of the arguments presented in its original Appeal Brief filed March 16, 2006. In order to facilitate review by the Board, Appellant also presents the following concise argument.

In Appellant’s previously filed Appeal Brief, Appellant questioned why one of skill in the art would conclude that inhibiting the natural MAO-B activity of lymphocytes and granulocytes would have beneficial results for an organism based on the art cited by the Examiner. One of the cited references, Balsa, discloses that lymphocytes and

granulocytes in pig blood, when properly functioning in the immune system, have MAO-B activity. Balsa does not disclose what effect inhibiting the MAO-B activity of lymphocytes and granulocytes would have on the immune system. The Examiner has failed not only to identify any passage in the cited references which suggest that inhibiting the normal MAO-B activity in lymphocytes and granulocytes would have a beneficial effect, but also to provide any scientific evidence to that effect. Instead of a scientific answer to this question, the Answer makes the following conclusory response: “one of any ordinary skill in the art would have expected DMS [] to be effective in inhibiting the MAO-B activity of lymphocytes and granulocytes, that play a key role in immune system function, which in turn modulates the immune and provide treatment for the conditions associated with immune system dysfunction.” Answer, p. 14.

The Examiner has presented *no evidence* and *no argument* to support the incorrect assertion that one of skill in the art would expect inhibiting MAO-B in lymphocytes and granulocytes to treat conditions produced by immune system dysfunction associated with reduced levels of γ -interferon production. This failure is fatal to the rejection. Without this expectation, a person of ordinary skill in the art would not have been motivated to combine the cited references, nor anticipate that any such combination would be successful. Therefore, the Examiner continues to use hindsight reconstruction to supplement the disclosures of these references to find the claimed methods obvious.

In light of this failure, Appellant respectfully requests that the Board overturn the obviousness rejection.

C. Conclusion

Appellant respectfully submits that based on the foregoing observations and arguments, all pending claims are enabled and patentable. It is therefore respectfully requested that the Board overturn all of the Examiner's rejections.

Respectfully submitted,

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Date: August 7, 2006

VIII. CLAIMS APPENDIX

Claims 1-25 (Canceled).

Claim 26. (Previously presented) A method of treating a condition in a mammal produced by immune system dysfunction that is associated with reduced levels of γ -interferon production, which comprises administering to the mammal the R(-) enantiomer of desmethylselegiline, or a pharmaceutically acceptable acid addition salt thereof, at a daily dose, administered in a single or multiple dosage regimen, of at least about 0.015 mg, calculated on the basis of the free secondary amine, per kg of the mammal's body weight, wherein the administration of the R(-) enantiomer of desmethylselegiline or a pharmaceutically acceptable acid addition salt thereof leads to an increase in γ -interferon production in the mammal.

Claims 27-33 (Canceled).

Claim 34. (Previously presented) The method of claim 26, wherein said R(-) enantiomer of desmethylselegiline is in a substantially enantiomerically pure state.

Claim 35. (Previously presented) The method of claim 26, wherein the condition produced by immune system dysfunction is caused by infectious disease.

Claim 36. (Previously presented) The method of claim 26, wherein the immune system dysfunction is age-dependent.

Claim 37. (Previously presented) The method of claim 26, wherein the condition produced by immune system dysfunction is AIDS.

Claim 38. (Previously presented) The method of claim 26, wherein the condition produced by immune system dysfunction is cancer.

Claim 39. (Previously presented) The method of claim 26, wherein the condition produced by immune system dysfunction is in response to a vaccine.

Claim 40. (Previously presented) The method of claim 26, wherein the daily dose is between about 0.5 mg/kg and about 1.0 mg/kg.

Claim 41. (Previously presented) The method of claim 26, wherein the daily dose is at least about 1.0 mg/kg.

Claim 42. (Previously presented) The method of claim 26, wherein the mammal is a human.

Claim 43. (Previously presented) A method of treating a condition in a mammal produced by immune system dysfunction caused by cancer chemotherapy which is associated with reduced levels of γ -interferon production, which comprises administering to the mammal the R(-) enantiomer of desmethylselegiline, or a pharmaceutically acceptable acid addition salt thereof, at a daily dose, administered in a single or multiple dosage regimen, of at least about 0.015 mg, calculated on the basis of the free secondary amine, per kg of the mammal's body weight, wherein the administration of the R(-) enantiomer of desmethylselegiline or a pharmaceutically acceptable acid addition salt thereof leads to an increase in γ -interferon production in the mammal.

Claim 44. (Previously presented) The method of claim 43, wherein the R(-) enantiomer of desmethylselegiline is in a substantially enantiomerically pure state.

Claim 45. (Previously presented) The method of claim 43, wherein the mammal is a human.

Claim 46. (Previously presented) A method of treating a condition in a mammal produced by immune system dysfunction that is associated with reduced levels of γ -interferon production, which comprises administering to the mammal the R(-) enantiomer of desmethylselegiline, or a pharmaceutically acceptable acid addition salt thereof, wherein the administration of the R(-) enantiomer of desmethylselegiline or a pharmaceutically acceptable acid addition salt thereof leads to an increase in γ -interferon production in the mammal.

Claim 47. (Previously presented) The method of claim 46, wherein the R(-) enantiomer of desmethylselegiline is in a substantially enantiomerically pure state.

Claim 48. (Previously presented) The method of claim 46, wherein the mammal is a human.

Claim 49. (Previously presented) The method of claim 46, wherein the R(-) enantiomer of desmethylselegiline or a pharmaceutically acceptable acid addition salt thereof is administered orally.

Claim 50. (Previously presented) The method of claim 46, wherein the R(-) enantiomer of desmethylselegiline or a pharmaceutically acceptable acid addition salt thereof is administered non-orally.

Claim 51. (Previously presented) The method of claim 46, wherein the R(-) enantiomer of desmethylselegiline or a pharmaceutically acceptable acid addition salt thereof is administered parenterally.

Claim 52. (Previously presented) The method of claim 46, wherein the R(-) enantiomer of desmethylselegiline or a pharmaceutically acceptable acid addition salt thereof is administered transdermally.

Claim 53. (Previously presented) The method of claim 46, wherein the R(-) enantiomer of desmethylselegiline or a pharmaceutically acceptable acid addition salt thereof is administered buccally or sublingually.

Claim 54. (Previously presented) The method of claim 46, wherein the R(-) enantiomer of desmethylselegiline or a pharmaceutically acceptable acid addition salt thereof is administered intravenously.

Claim 55. (Previously presented) The method of claim 46, wherein the R(-) enantiomer of desmethylselegiline or a pharmaceutically acceptable acid addition salt thereof is administered subcutaneously.

Claim 56. (Previously presented) The method of claim 46, wherein the R(-) enantiomer of desmethylselegiline or a pharmaceutically acceptable acid addition salt thereof is administered intra-peritoneally.

Claim 57. (Previously presented) The method of claim 46, wherein the R(-) enantiomer of desmethylselegiline is administered at a daily dose of at least about 0.015 mg/kg of the mammal's body weight, calculated on the basis of the free secondary amine.

Claim 58. (Previously presented) The method of claim 46, wherein the condition produced by immune system dysfunction is caused by infectious disease.

Claim 59. (Previously presented) The method of claim 46, wherein the immune system dysfunction is age-dependent.

Claim 60. (Previously presented) The method of claim 46, wherein the condition produced by immune system dysfunction is AIDS.

Claim 61. (Previously presented) The method of claim 46, wherein the condition produced by immune system dysfunction is cancer.

Claim 62. (Previously presented) The method of claim 46, wherein the condition produced by immune system dysfunction is in response to a vaccine.

IX. EVIDENCE APPENDIX

The following reference was cited in and provided with Appellant's Appeal Brief filed March 16, 2006.

Billiau, A., *Interferon- γ : Biology and Role in Pathogenesis*, ADV. IMMUNOL. 62:61-130 (1996)

X. RELATED PROCEEDINGS APPENDIX

As explained in Section II, a Notice of Allowance has been received for each of the related applications identified in Section II. No decisions were rendered by any court or the Board in those applications.